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INVITED REVIEW

What is the role of parenteral nutrition in the management of the patient with severe acute pancreatitis?

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Abstract

Severe acute pancreatitis often presents as a complex critical illness associated with a high rate of infectious morbidity, multiple organ failure, and in-hospital mortality. Breakdown of gut barrier defenses, dysbiosis of intestinal microbiota, and exaggerated immune responses dictate that early enteral nutrition (EN) is preferred over parenteral nutrition (PN) as the primary route of nutrition therapy. EN, however, is not feasible in all cases because of intolerance, risk of complications, or a direct contraindication to enteral feeding. For these patients, PN can be provided in a manner that is safe, is metabolically appropriate, and follows the principles of modern critical care nutrition. Adherence to goal-directed fluid resuscitation, provision of trophic doses of PN to meet 20%–25% of protein and/or calorie requirements through the acute phases of illness, use of less-inflammatory intravenous lipid emulsions, and close monitoring of electrolytes, triglyceride levels, and signs of refeeding syndrome all serve to optimize the response to this route of nutrition support. For these reasons, prescribing PN remains an important strategy in the management of this difficult population of patients.

KEYWORDS

acute pancreatitis, enteral nutrition, fluid resuscitation, inflammation, intolerance, parenteral nutrition

INTRODUCTION

For decades, strategies in the management of acute pancreatitis required that patients were made nil per mouth, placed on gut rest, started automatically on parenteral nutrition (PN), given prophylactic antibiotics, and restricted from receiving opioid analgesia, all of which have been invalidated by more recent literature.[1,2] A majority of patients representing 65%–70% of those requiring hospitalization for acute pancreatitis have mild disease severity, have an uncomplicated hospital course, and do not require specialized nutrition therapy.[1] In fact, these patients can often be managed by oral diet alone, directed by the patient's wishes. Another 20%–25% of patients presenting for hospitalization have moderate acute pancreatitis, characterized by pancreatic injury, fluid collections, and necrosis. In such patients, moderate pancreatitis is defined by transient organ failure, involving one or more of three organ systems (respiratory, renal, or circulatory), which resolves within 48 h.[1] Even these

patients with moderate disease severity usually require mainly fluid resuscitation and analgesia without the need for specialized nutrition therapy.[3] A remaining 5%–10% of patients have severe acute pancreatitis (SAP), defined by persistent failure of one of the three organ systems for >48 h.[1] Such patients tend to have a hospital length of stay >4 weeks and a mortality rate that can approach 30%–50%.[1,4]

Eighty percent of the deaths in those patients with SAP are associated with sepsis from organisms of enteric origin.[3] Impaired pancreatic endocrine and/or exocrine function because of massive necrosis occurs in 20%.[4] Chronic pancreatitis develops in 10% of patients after the first episode of SAP but increases in frequency to 33% for those patients with recurrent SAP.[4] Data accumulating over the past three decades indicate that loss of gut barrier defenses, immune dysregulation, and intestinal microbial dysbiosis exacerbate disease severity in acute pancreatitis, worsen outcomes, and increase complications.[5] These patients appear critically ill, require placement in an intensive care unit (ICU), and need provision of specialized nutrition therapy via the enteral or parenteral route.

Compared with patients with mild acute pancreatitis, those with moderate pancreatitis have a 4-fold increase in intestinal permeability and those with SAP have a 4-fold increase above that.[6] Dysbiosis of gut microbiota affects both the etiology and severity of acute pancreatitis via gut barrier disruption, a local and/or systemic inflammatory response, bacterial translocation, and an altered regulatory role of microbial metabolites.[3,5,7] In fact, the dysbiosis is considered a "second strike" causing systemic gut-derived infection in acute pancreatitis. Loss of butyrate-producing organisms exacerbates acute necrotizing pancreatitis.[5] Although it is not clear whether the changes in the intestinal microbiota are causative or reactive in pancreatitis, both alpha and beta diversity are diminished as commensal organisms such as Actinobacteraciae, Bifidobacterium, and *Lactobacillus* diminish; opportunistic organisms such as Bacteroidetes and Proteobacteria proliferate; and an increase in the Firmicutes to Bacteroidetes ratio is seen.[5]

Damage to pancreatic acinar cells causes the release of its contents into the systemic circulation (microbial DNA, adenosine triphosphate, heat shock protein-70, and cytosolic protease caspase-1), which act as proinflammatory signaling molecules.[8] The immune dysregulation that results is characterized by increases in proinflammatory T_H1 and T_H17 lymphocytes and a parallel decrease in Paneth cell antimicrobial defensins.[9]

Evidence found to coincide with much of these data suggests that the provision of enteral nutrients may protect against and/or reverse many of these changes within the gastrointestinal (GI) tract.[4] Even in mild acute pancreatitis, there is a role for oral feeding started early to help decrease hospital length of stay, reduce cost of medical care, and avoid abdominal pain and bloating without increasing complications, infection, or mortality.[4,10] As long as it is well tolerated, early oral feeding may decrease the intensity and duration of pain and reduce the need for opioid analgesia.[1] In more severe cases, use of early enteral nutrition (EN) for patients with severe SAP reduces ICU and/or hospital length of stay, infectious complications, multiple organ failure, need for surgical intervention, severity of the systemic inflammatory response syndrome (SIRS), and in some studies, even mortality rates compared with similar patients receiving PN or who continue to receive nothing by mouth.[4,11,12] The incidence of at least one organ system failing in SAP increases from 21% when early EN is initiated, up to 81% when EN is delayed.[13] Such a benefit from early EN may be diminished in those patients in whom SAP is combined with septic shock or an overly severe SIRS.[13]

This growing body of literature substantiates the preference for use of EN over PN in critically ill patients with SAP. However, not all patients in an ICU setting tolerate early EN. As a result, clinicians are unclear as to when PN should be used in such circumstances. Unfortunately, much dogma exists regarding the indication, timing of initiation, safety, fluid volume, choice of macronutrients, and addition of parenteral supplements involved with the provision of PN in SAP. This manuscript seeks to sort through conflicting treatment strategies proposed in the literature in an effort to delineate the current role for PN in managing the complex population of patients with SAP.

CONTROVERSIAL BELIEFS ASSOCIATED WITH USE OF EN AND/OR PN IN SAP

Much dogma related to the management of SAP in the past was based on theoretical concerns, many of which have been subsequently dismissed as increasing supportive data have accumulated. In the absence of confirmed infection within the gland, prophylactic antibiotics failed to improve outcomes and more often resulted in the emergence of resistant organisms.[4,14,15] Although opioid narcotics such as morphine or demerol stimulate contraction of the sphincter of Oddi, their use was found to be safe in SAP without exacerbating inflammation.[1] The need for "gut rest" and the absence of any luminal nutrients was based on the documented defects of exaggerated sustained stimulation of pancreatic exocrine function and a secretory defect that trapped activated pancreatic enzymes within the gland, leading to

autodigestion of the acinar cells and accelerated proinflammatory responses.[16] Studies using labeled carbon showed that activation and production of pancreatic enzymes in acute pancreatitis still occurred in response to the luminal infusion of enteral nutrients, but the response was muted with lower systemic levels of the enzymes because of the secretory defect.[17] However, activation and release of the enzymes occurred at some subclinical level because it was shown that feeding by the enteral route was feasible without exacerbating inflammation within the gland.[17]

Early controversy existed regarding the level of infusion of enteral nutrients within the GI tract that was considered safe from exacerbating inflammation for patients with SAP. Based on his own work and that of others generated by studies with labeled carbon, enzyme activation, and variable tube placement within the GI tract, O'Keefe concluded that the delivery of luminal nutrients had to be infused 40 cm or more beyond the ligament of Treitz to avoid increasing pancreatic inflammation.[17] In the first randomized controlled trial (RCT) of EN vs PN in acute pancreatitis, an incident involving one patient in which the tip of the feeding tube was displaced from the jejunum back to the stomach, causing a dramatic SIRS response, was interpreted to indicate that only jejunal feeding was safe in SAP.[18] Multiple subsequent RCTs comparing gastric with postpyloric feeding in SAP (in which pain, energy delivered, and diarrhea were equivalent) refuted the interpretation of O'Keefe's earlier work and indicated that the patient with the displaced feeding tube was an outlier.[17,18]

Misinterpretation of the PYTHON trial comparing "on demand" oral diet for 5 days (patients asked if they wanted to start a per os diet) with early EN by tube feeding initiated within 24 h of admission led to the subsequent belief that a decision on starting nutrition therapy could be delayed until after the first 5 days of hospitalization.[19] Although the major combined end point of the study (death and infectious morbidity) was no different between the two groups, over 80% of the patients were managed on the ward and were not critically ill in an ICU setting. Such patients rarely require specialized nutrition therapy, and thus, results did not apply to those patients with SIRS severe enough to warrant critical care, placement in an ICU, and need for early EN.[19]

More dogma involved the notion that significant complications of SAP (such as pseudocysts, walled-off necrosis, pancreatic ascites, etc) required cessation of EN and initiation of PN.[15] The evolution of minimally invasive therapy and the advocation of a step-up approach to surgical intervention with laparoscopic or robotic debridement of retroperitoneal pancreatic necrosis decreased the need for PN from the days of open pancreatic debridement in which PN was used more commonly.[20] Further theoretical concern existed for use of intravenous lipid emulsions (ILEs) with PN in SAP, believing that the intravenous lipid would directly stimulate pancreatic exocrine function or cause hypertriglyceridemia, leading to worsening clinical severity.[16] Such concern was surprising because an early 1984 publication confirmed that intravenous mixed amino acids and lipid did not stimulate exocrine pancreatic secretion.[21] Similarly, the addition of calcium to the PN preparation was avoided out of fear of direct pancreatic stimulation. In the absence of hypercalcemia or hypertriglyceridemia, the presence of protein, fat, or calcium in the PN regimen per se was shown not to exacerbate inflammation.[15]

WHAT ARE THE INDICATIONS FOR USE OF PN IN SAP?

Close to 75% of patients with SAP tolerate early nasoenteric EN.[22] However, EN is not always feasible because of issues of intolerance, risk of complications, or presence of a direct contraindication to enteral feeding. Approximately 20% of patients with SAP have a contraindication to EN.[23,24] Absolute contraindications include uncontrolled shock, hypoxemia, hypercapnia, severe acidosis, abdominal compartment syndrome (ACS), bowel obstruction, peritonitis, or intestinal ischemia.[25] More relative contraindications include prolonged ileus, high gastric residual volumes >500 ml, upper GI bleeding, or a high-output fistula without distal feeding access.[25] Typically, those conditions in which PN is commonly used in SAP include severe ileus with abdominal distention, bloating, vomiting, or duodenal compression by a pseudocyst or inflammatory swelling in the head of the pancreas. Systemically, SAP tends to affect both major vessels and the microcirculation with increased capillary permeability, decreased splanchnic perfusion, extensive coagulopathy, and risk for mesenteric ischemia.[26] Concern for potential ischemia with the use of EN is thus a common condition in which PN is used. Less common is the condition of pancreatitis with severe hypertriglyceridemia, in which one management strategy is to initiate gut rest with cessation of oral intake and placement on PN without lipid emulsion.

Several conditions related to the management of patients with SAP that concerned clinicians in the past and were interpreted to indicate the need for cessation of EN have now been shown not to be an automatic mandate for switching to PN. Such conditions include elevated intra-abdominal pressure, sepsis complicating SAP,

open abdomen following aggressive surgical necrosectomy, postoperative fistula following pancreatic surgery, and midbody necrosis of the gland with disruption of the pancreatic duct and a tail that is still capable of producing pancreatic enzymes.[25,27,28] Normal intra-abdominal pressure is 5–7 mm Hg, with intra-abdominal hypertension diagnosed when pressures exceed 12 mm Hg.[25] EN is well tolerated when intra-abdominal pressures are <15 mm Hg but may need to be held when pressures exceed 20 mm Hg or there is clear evidence of ACS.[25] Although it sounds counterintuitive, EN may help prevent elevated intra-abdominal pressure because of its effect on increasing GI motility, decreasing bowel wall edema, and hastening resolution of swelling and inflammation within the pancreatic gland. Early initiation of EN within 24 h has been shown to reduce elevated intra-abdominal pressure at a faster rate compared with EN initiated after the first week of hospitalization.[29] EN has been shown to be well tolerated in cases of open abdomen, and its use compared with PN is associated with a mortality benefit, fewer complications, and a higher fascial closure rate.[25] Especially with the trend toward minimally invasive necrosectomy, EN can usually be initiated early in the postoperative period without the necessity for switching to PN. Use of EN in patients with early postoperative pancreatic fistulas has been shown to be associated with higher closure rates and shorter time to closure compared with use of PN.[30] Although midbody necrosis and disruption of the pancreatic duct often does require use of PN for nutrition therapy, its use is indicated only by documented intolerance to EN with greater pain, worsening inflammation, abdominal distention, or increasing pancreatic ascites.

As a result of these factors discussed above, exclusive PN is typically required in only 20%–25% of cases of SAP.[22] Because of problems related to fuel use and anabolic resistance at the height of the SIRS, guidelines have recommended that initiation of PN be delayed for 4–5 days following admission to the ICU past the peak of maximum pancreatic inflammation.[14,24,31] Advances in the delivery of PN, control of hyperglycemia, and maintenance of the intravenous access site may allow for earlier initiation, especially in cases of substance abuse, poor dietary habits, weight loss, or high likelihood of malnutrition present before admission. Obese patients with SAP may be at higher risk of increasing their need for earlier initiation of PN because their pathophysiology shows evidence of upregulated lipolysis of visceral fat, resulting in mitochondrial abnormality and increasing pancreatic necrosis.[32]

The frequency with which supplemental PN is added for a patient with SAP who is already receiving EN is poorly documented. The variable intolerance and degree of ileus necessitating supplemental PN is difficult to quantify. The delivered amount or volume of EN needed to maintain gut barrier defenses and support the commensal microbiome is not clear. Recent evidence further suggests that low-dose trophic amounts of calories and protein provided early in the course of critical illness compared with full-dose feeding (closer to meeting requirements) is associated with reduced bowel ischemia, lower ICU mortality rates, less prokinetic use, shorter time to wean from vasopressor support and mechanical ventilation, better glycemic control, and fewer GI complications.[33] The lack of a defined benefit on clinical outcomes in the literature, especially in SAP, adds further difficulty to the decision to initiate supplemental PN.[34] The best parameters to direct clinical decision-making, derived from guidelines in critical care, are to withhold supplemental PN over the first 7 days following admission to the ICU and only initiating such therapy when the amount of EN delivered is still meeting <60% of protein and/or calorie requirements.[24,31]

PN DELIVERY ISSUES

Several issues are clinically relevant to the delivery of PN, some of which are unique to the patient with SAP but most of which are related simply to the care of the individual with critical illness. Following societal guidelines for critical care seems appropriate for this patient population. A number of factors related to fluid resuscitation can easily influence the course of hospitalization for the patient with SAP.[4] Insufficient or slow fluid replacement has been shown to adversely affect organ function, resolution of the SIRS, and duration of hospitalization.[4] On the other hand, overly aggressive fluid resuscitation may contribute to elevated intra-abdominal pressure and ACS because of bowel wall edema, hypoalbuminemia, ascites, and pancreatic edema.[4] Rapid hemodilution to a hematocrit <35% was shown to be associated with increased sepsis, infectious complications, and death compared with slow hemodilution in which the hematocrit remained >35%.[35] Goal-directed fluid resuscitation has replaced the tendency in the past for overzealous fluid volume delivery.[36] Typically, a rate of 5–10 ml/kg/h is initiated to achieve a goal defined by several parameters: an increase in mean arterial pressure to 65–85 mm Hg, a heart rate <120 bpm, hematocrit in the range 35%–45%, and a urine output of >0.5–1.0 ml/kg/h.[1,4,36] In one RCT, goal-directed moderate fluid resuscitation caused fluid overload in fewer patients than the traditional aggressive approach (6.3% vs 20.5%, $P = 0.004$).[36] In another RCT, a higher rate of volume resuscitation of 10–15 ml/kg/h was associated with a greater frequency of infectious complications and higher

mortality rates compared with a rate of 5–10 ml/kg/h.[37] Use of crystalloid (saline or lactated Ringer's solution) is recommended over the use of colloid (dextran, albumin, or fresh frozen plasma).[4] Use of hydroxyethyl starch as a colloid for fluid resuscitation in critical illness has been associated with an increase in acute renal failure and higher mortality rates.[4] In a separate RCT, use of lactated Ringer's solution compared with normal saline led to lower levels of C-reactive protein (CRP) and facilitated faster resolution of SIRS.[38]

As PN is initiated in the patient with SAP, clinicians need to watch for evidence of refeeding syndrome (RFS), especially in patients with a history of substance abuse, weight loss, poor dietary habits, or chronic pancreatitis. Risk for developing RFS is less with provision of PN compared with EN, the latter of which stimulates glucagon-like peptide-1 or incretin-augmenting insulin release, causing greater electrolyte shifts.[39] Serum calcium levels should be monitored closely, and serum triglyceride levels should be controlled to <400 gm/dl. Control of hyperglycemia is more difficult with provision of PN compared with EN in SAP.[18] Standard preparations of intravenous multivitamins and multiple trace elements should be provided. Lack of consistent evidence for the provision of supraphysiologic doses of selenium, vitamin D, vitamin C, or any other micronutrients precludes their use in the critically ill patient with SAP.[24]

PN should be initiated at trophic doses approximating 25% of calorie and/or protein requirements through the acute phases of critical illness in SAP, following the basic principles of critical care nutrition by decreasing risk of RFS, minimizing risk for overfeeding (in which PN is combined with endogenous hepatic glucose production), reducing demand on failing mitochondria, lessening inhibition of autophagy, and avoiding excessive fluid intake.[33] Doses should be advanced to meet requirements as the patient shows signs of progress to recovery, as evidenced by a decrease in SIRS, dropping CRP levels, achievement of hemodynamic stability, reduced pain, increasing tolerance for EN, and an emerging sensation of hunger.[40] The goal for protein delivery should remain somewhat conservative at 1.3–1.5 gm/kg/day. Acute kidney injury has been shown to occur in 7.9%–18.4% of patients with SAP, and high protein intake >1.8 g/kg/day has been shown to be harmful in those patients.[41] Although RCTs have shown a benefit of intravenous glutamine added to PN in patients with SAP, its use in the critically ill patient is controversial because of some evidence of harm (increased mortality rates), especially in a setting of acute kidney injury or need for steroid therapy.[42,43] Use of an ILE has been shown to be safe for patients with SAP, but consideration should be given for use of a less-inflammatory fat mixture (such as soy, medium-chain triglyceride, olive oil, and fish oil) over the more inflammatory pure soy-based Intralipid (Fresenius Kabi).[16] The development of severe hypertriglyceridemia no longer requires gut rest and the avoidance of any oral intake. Intravenous insulin combined with fluid resuscitation helps reduce triglyceride levels. If an inadequate response is not achieved, plasmaphoresis or placement on fibrate therapy may be required. Modifying the PN regimen to have minimal lipid content is another but rarely needed alternative strategy.

Patients should continue to be monitored as they progress through the course of their ICU and subsequent ward hospitalization. Clinicians should watch for the opportunity to initiate EN, which may be delayed in the presence of hemodynamic instability, repeated trips to the operating room, or sequential retroperitoneal laparoscopic debridement of pseudocysts or necrosis. Once EN is initiated, PN may be stopped when the EN is providing >60% of protein/calorie requirements.[44] Pancreatic exocrine insufficiency occurs in >50% of patients hospitalized for acute pancreatitis, but this incidence falls after patients are discharged and inflammation within the gland resolves.[1] Pancreatic enzyme replacement therapy (PERT) should be considered in patients with >50% necrosis.[1]

Future potential nutrition approaches for PN in SAP may include use of a pure fish oil ILE, containing high doses of anti-inflammatory eicosapentaenoic acid and docosahexaenoic acid, as a treatment to enhance resolution.[16] Parenteral delivery of ω-3 fatty acids was shown in one meta-analysis in SAP to reduce mortality rates, infection, and ICU and hospital length of stay, as well as to down-regulate release of CRP compared with controls receiving soy-based ILE.[45] Possibly, giving specialized proresolving molecules, end-products of fish oil metabolism (such as resolvins, maresins, and protectins) that actively curtail inflammation, may be a consideration as well.[46] Adding leucine to enhance protein synthesis might be a valuable strategy in the later phases of SAP as the patient is moving toward recovery.[47]

CONCLUSIONS

Specialized nutrition therapy is rarely required for the majority of patients with mild to moderate acute pancreatitis, and the provision of oral diet alone in these patients may shorten length of hospitalization and reduce overall medical cost. For those fewer patients with SAP, EN is preferred over PN as the primary route of nutrition therapy. EN will not be feasible in a

significant percentage of cases, however, because of a clear intolerance, an increased risk of complications, or the presence of a contraindication to enteral feeding. PN may be given safely, but its delivery should be designed to meet the principles of modern critical care nutrition with goal-directed fluid resuscitation and provision of near trophic doses throughout the acute phases of critical illness.

Changes in the management and delivery of PN make it safer and more metabolically tolerated, with the use of mixed lipid emulsions, better glucose control, improved management and oversight of the central line access, continued attempts to deliver small-volume EN to protect barrier function, and the avoidance of overfeeding. PN continues to serve as a useful tool in specific cases of SAP.

AUTHOR CONTRIBUTIONS

Stephen A. McClave and Robert G. Martindale equally contributed to the conception and design of the paper, Steve McClave and Robert Martindale contributed to the acquisition and analysis of the data, Stephen A. McClave and Robert G. Martindale contributed to the interpretation of the data, and Stephen A. McClave drafted the article. All authors critically revised the article, agree to be fully accountable for ensuring the integrity and accuracy of the work, and for reading and approving the final article.

CONFLICT OF INTEREST STATEMENT

Robert G. Martindale is an education consultant for Nestlé and Abbott and an educational/research consultant for Fresenius Kabi. Stephen A. McClave is an educational consultant for Nestlé and Abbott, is an educational/research consultant for Fresenius Kabi, and is on a clinical advisory board for Avanos.

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